IV. Rejection of Claim 9 Under 35 U.S.C. § 112, Second Paragraph

Claim 9 alone remains rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite in reciting the phrase "chimeric antibody" (second Action at page 4). All other claims are free from this rejection. Applicants respectfully traverse, as set forth in their first response, which is incorporated herein by reference. Applicants respond to the second Action at page 4 as follows.

Importantly, it is noted that the first Action itself evidenced a clear understanding of this term (*e.g.*, first Action at page 5, Item 7). As the United States Patent and Trademark Office clearly understands the term in question, there can be no *prima facie* question under 35 U.S.C. § 112, second paragraph. Applicants explained this issue in their first response, which has not been addressed in the second Action. This is strong evidence that the original rejection was without merit and is overcome.

Moreover, the second Action's position that a term of art can routinely appear in the claims of multiple hundreds of issued U.S. patents without those of ordinary skill in the art understanding the meaning of such a term is untenable. 35 U.S.C. § 112, second paragraph clearly requires that all claim terms be understandable by those of ordinary skill in the art before a claim can issue. Therefore, for the phrase "chimeric antibody" to appear in the claims of over 600 issued U.S. patents, it must, by definition, be understood by those of ordinary skill in the art.

The rejected term also occurs in the same context in the claims issued in the parent, U.S. Patent No. 6,703,020 ("the '020 patent"), and numerous related patents having the same specification (Patent Nos. 6,342,219; 6,524,583; 7,056,509; 6,887,468; 6,342,221; 6,676,941; and 6,416,758). As to the second Action's position that the use of the same term in a related patent application is not determinative of the issue, such a position is erroneous and clearly in contradiction of case law from the Federal Circuit.

The present application has the same specification, and claims priority to the same provisional application as the '020 patent (as do the other patents listed above). Issuance of the '020 and other patents, including the same claim language as currently rejected, and yet earlier determined to be patentable, thus compels a finding of patentability for the present claims. 35 U.S.C. § 282; *Biovail Corp. International vs. Andrx Pharmaceuticals Inc.*, 57 USPQ2d 1813 (Fed. Cir. 2001). Although each application is considered on its own merits, as the specifications are the same, the priority dates are the same, and the claim language at issue is the same, the merits are the same:

> "When multiple patents derive from the same initial application, the prosecution history regarding claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contain same claim limitation".
>
> *Biovail Corp. International vs. Andrx Pharmaceuticals Inc.*, 57 USPQ2d 1813, 1816 (Fed. Cir. 2001).

Furthermore, the terms "chimeric" and "chimera", as used in the antibody field, are shown to be clearly understandable to those of ordinary skill in the art as they are used by the United States Adopted Names (USAN) Council to name monoclonal antibody biologics.

The purpose of the USAN Council, sponsored by the American Medical Association (AMA), is to select simple, informative and unique nonproprietary names for drugs by establishing logical nomenclature classifications based on pharmacological and/or chemical relationships (**Exhibit A**). The USAN Council also aims for global standardization and unification of drug nomenclature to ensure that drug information is communicated accurately and unambiguously on an international level (**Exhibit A**). This is achieved by, *e.g.*, working closely with the International Nonproprietary Name (INN) Programme of the World Health Organization (WHO) (**Exhibit A**).

The USAN Council has established guidelines for naming "biologics", so that USAN can be assigned to biological products such as insulins, interferons, interleukins, growth hormones, colony-stimulating factors, cytokines, *monoclonal antibodies* and coagulation factors (**Exhibit A**). The suffix *-mab* is used to name monoclonal antibodies and fragments. The USAN Council then assigns the following letters as product source identifiers (**Exhibit A**):

u = human	e = hamster
o = mouse	i = primate
a = rat	xi = chimera
Zu = humanized	

It is explained that these identifiers are used as infixes preceding the *-mab* suffix stem (**Exhibit A**), for example:

- umab (human)	- ximab (chimera)
- omab (mouse)	- zumab (humanized)

It can thus be seen from **Exhibit A** that the USAN Council, working on behalf of internationally renowned bodies such as the American Medical Association and the World Health Organization, uses the term "chimera" in reference to monoclonal antibodies entirely without qualification. Therefore, as the very agency responsible for assigning informative names to monoclonal antibodies uses the term chimera without further explanation, this is definitive evidence that the terms "chimeric" and "chimera", as used in the antibody field, are clear and definite to those of ordinary skill in the art.

The § 112, second paragraph rejection is thus overcome and should be withdrawn.

V. Objection to Claims 49 and 50

The second Action next objects to claims 49 and 50 as essentially duplicates of claims 48 and 47, respectively. Although Applicants respectfully traverse, the objection is overcome.

As previously drafted, claims 48 and 47 were dependent claims, the subject matter of which was also reflected in independent claims 49 and 50. It is routine in U.S. patent practice for the same or essentially the same subject matter to be represented in separate dependent and independent claims. Accordingly, the objection to claims 49 and 50 is in error and should be withdrawn[2].

The objection is thus overcome and should be withdrawn.

VI. Rejection of Claims 10, 48 and 49 Under 35 U.S.C. § 112, First Paragraph

Claims 10, 48 and 49[3] are next rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enabling support in the specification. All other claims are free from this ground of rejection[3]. Applicants respectfully traverse, as set forth in their first response, which is incorporated herein by reference. Applicants additionally respond as follows.

A. Enablement, and Rejection Overcame in the Parent and Related Patents

In Applicants' first response, it was pointed out that enabling support for claim 10 has already been established with the issuance of the same claim from the immediate parent application, now the '020 patent. Indeed, the same claim issued after an analogous enablement rejection was entered and overcome in the '020 patent. The same claims also issued in U.S. Patent Nos. 6,342,219; 6,524,583; 7,056,509; 6,342,221; 6,676,941; and 6,416,758, which each have the same specification as the present case. U.S. patents are presumed valid under 35 U.S.C. § 282. Issuance of patents containing the same claim language from the immediate parent and related patents thus compels a finding of enabling support and patentability for the present claims. *Biovail Corp. International vs. Andrx Pharmaceuticals Inc., supra.*

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[2] In any event, claim 49 now recites different subject matter than claim 48.

[3] Claim 49 no longer includes the complained of language.

The foregoing important points have not been addressed in the second Action. This evidence alone is dispositive that the present rejection is without merit and overcome.

B. Claim 10 is Enabled, According to the Second Action

Claims 10 and 48 recite that the antibody of the immunoconjugate "comprises at least a first variable region that includes an amino acid sequence region having the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:9". The transitional phrase "comprising" means that the named elements are essential, but other elements may be added. *Genentech Inc. v. Chiron Corp.*, 42 USPQ2d 1608, 1613 (Fed. Cir. 1997). Thus, claim 10 clearly covers antibodies that comprise a variable region including the amino acid sequence of SEQ ID NO:7 and a variable region including the amino acid sequence of SEQ ID NO:9.

The second Action bridging pages 4 and 5 indicates that antibodies comprising variable regions that include the amino acid sequences of SEQ ID NO:7 and SEQ ID NO:9 are enabled. Thus, claims 10 and 48 comply with the Action's assessment of enabling support and the rejection is consequently improper. Applicants explained this issue in their first response. Although the second Action at page 8 paraphrases Applicants' position, no reply is offered. This again shows that the rejection is unfounded.

Indeed, the rejection continues to be based on an improper reading of claims 10 and 48 as meaning only SEQ ID NO:7 or SEQ ID NO:9, but somehow excluding both (*e.g.*, second Action at page 7). Such a reading is inconsistent with U.S. claim interpretation, as claims 10 and 48 clearly cover antibodies comprising both SEQ ID NO:7 and SEQ ID NO:9, and are thus allowable according to the reasoning in the second Action itself.

After all, it would be possible for the Office to read almost any claim on inoperative embodiments. For example, the Office could assert that claims 10 and 48 read on the invention as practiced on Mars, because the claims do not specifically recite conducting the invention on

Earth. Such analyses are improper. It is not the function of the claims to specifically exclude possible inoperative embodiments. *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.*, 224 USPQ 409 (Fed. Cir. 1984).

Accordingly, the present rejection is improper and overcome on this ground alone. However, the rejection is unfounded even as to an antibody containing only SEQ ID NO:7 or SEQ ID NO:9, without the other, as set forth below.

C. Claim 10 is Enabled, According to Chain Shuffling

As set forth above, claims 10 and 48 recite that the antibody of the immunoconjugate comprises at least a first variable region including the amino acid sequence of SEQ ID NO:7 or SEQ ID NO:9. In addition to wrongly excluding antibodies including SEQ ID NO:7 and SEQ ID NO:9, the second Action also seems to interpret these claims as being drawn to constructs in which the entire antibody has only the claimed Vh or Vκ region, and does not include any other Vh or Vκ region (*e.g.*, second Action at page 7, and particularly at page 8, which fails to address this point from Applicants' first response). Such an interpretation would also reflect an important error.

Properly construed, claims 10 and 48 cover an antibody that comprises (i) a Vh region of SEQ ID NO:7 together with a light chain other than SEQ ID NO:9, and (ii) a Vκ region of SEQ ID NO:9 together with a heavy chain other than SEQ ID NO:7. Such claims thus cover antibodies generated by the technique of chain shuffling, well-established in the art prior to the present invention and further disclosed in this application (see, *e.g.*, specification at Section B6, particularly at page 100, lines 13-18; '432 application at Section B5, particularly at page 65, lines 1-6; and U.S. patents incorporated into each application by reference). As with the single domain antibodies discussed below, chain shuffling has been practiced for well over a decade

and, by way of example only, one of the early seminal publications on chain shuffling is enclosed (Marks *et al.*, *BioTechnology*, 10:779-783, 1992; **Exhibit B**).

Not only has the production of chain shuffled clones been routine in the art for many years, a number of chain shuffled clones of antibodies in accordance with the present claims have actually been generated under the direction of the licensee of the present application and shown to have the recited binding capability (contrast to second Action at page 8). For example, certain chain shuffled clones share the heavy chain with a 2C3 motherclone, but have improved characteristics in comparison to the motherclone made by exchanging the light chain. Thus, not only is it *possible* to keep one variable region, exchange the other variable region and still produce antibodies with the original antigen-binding characteristics, as described in the literature, such antibodies have *actually been generated* (further information is currently confidential and proprietary material).

Therefore, the present rejection is overcome on this additional basis and should be withdrawn, notwithstanding that the rejection is still unfounded even as to other interpretations of the claims.

D. Claim 10 is Enabled, According to Single Domain Antibodies

As detailed above, the rejection of claims 10 and 48 is improper and overcome on various grounds. The rejection as applied to single domain antibodies is also unfounded and overcome, as set forth in Applicants' first response, which the second Action has not adequately addressed.

The second Action at page 7 repeats the allegation from the first Action that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody. As with the first Action, the second Action cites no support for such a position, which is contradicted by considerable scientific evidence (see below).

The second Action continues reliance solely on Rudikoff *et al.*, *Proc. Natl. Acad. Sci. USA*, 79:1979-1983, 1982 ("Rudikoff"), published 17 years before this application's priority date, and now 25 years ago. Applicants' first response pointed out that relying on a reference from 17 years before the invention in an attempt to establish non-enablement is not credible. The second Action again fails to address this issue.

Applicants' first response also pointed out that this aspect of the rejection entirely ignores the entire field of single domain antibodies, including all the patents and publications from the late 1980s to the present date.

In reply to this issue, all the second Action can do is to state that the listed exhibits could not be located with Applicants' first response. As shown by Applicants' correspondence of April 10, 2007, additional copies of Exhibits A-K, each of which were properly and timely submitted with Applicants' first response, have now been filed electronically. Upon consideration of the compelling evidence in Exhibits E, F, G, H and I, Applicants thus further expect the present rejection to be withdrawn.

In this regard, it is noted that the second Action at page 9 has not addressed the merits of this evidence. Applicants described in detail the content and pertinence of Exhibits E, F, G, H and I (even though copies apparently could not be located). In reply to which seminal references, company literature and issued U.S. patents, the second Action continues to allege, entirely without evidence, that all such references, company literature and issued U.S. patents are "exceptions", and that the state of the prior art remains as characterized by the Office relying solely on an article from 25 years ago discussing the unremarkable concept that changes in amino acid sequences may in *some* situations alter antigen-binding specificity (Rudikoff at abstract, emphasis as in original). Thus, Applicants' position remains essentially uncontested.

Indeed, it is hard to see how it could be contested that an entire field of single domain antibodies exists and prospers.

The § 112, first paragraph rejection is thus overcome and should be withdrawn.

VII. Rejection of Claims 3-6, 8-12, 25, 41, 42 and 46-51[4] Under 35 U.S.C. § 103(a)

Claims 3-6, 8-12, 25, 41, 42 and 46-51[4] are further rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over Brekken *et al.*, *Cancer Res.*, 58:1952-1959, 1998 ("Brekken") in view of Melton & Sherwood, *J. Natl. Cancer Inst.*, 88:153-165, 1996 ("Melton") and Presta *et al.*, *Cancer Res.*, 57:4593-4599, 1997 ("Presta").

Although Applicants respectfully traverse, the rejection as to most claims is overcome by following the second Action's guidance on priority. As to claims 49 and 41, Applicants maintain the traversal from their first response, which is incorporated herein by reference, and additionally respond as follows.

A. Claims Having Priority to April 28, 1999, According to the Second Action

The present rejection is largely predicated on not according the April 28, 1999 priority date to the rejected claims, such that Brekken could not be removed as prior art. Although Applicants respectfully disagree with the Office's initial holding in this regard, Applicants nonetheless very much appreciate the suggestion to perfect priority set forth in the second Action at page 3 (**Section III**). Namely, to recite in the claims "antibodies administered in conjunction with prodrugs that are cleaved by enzymes set free by necrotic processes" (second Action at page 3, two instances). Accordingly, and without acquiescing with the former denial of priority in any way, independent claims 5, 46, 50 and 51 have been amended to recite this exact language

[4]Although the second Action refers to claims 4-51, this is believed to mean claims 46-51.

from the second Action, which thus definitively establishes an April 28, 1999 priority date for all claims except claims 49 and 41.

B. Brekken is Not Available as Prior Art

In light of the second Action's guidance on priority (second Action at page 3, two instances), most claims are now agreed to have the priority date of the '432 application, *i.e.*, April 28, 1999. Brekken, which was published on May 01, 1998, is an article published on behalf of the present inventors less than a year before the present priority date, and is thus only potentially available under 35 U.S.C. § 102(a). Brekken has already been removed as prior art by entering the inventors' *Katz* declaration from the parent application into the present case.

As Brekken is removed as prior art, any § 103(a) rejection relying on Brekken is *prima facie* improper and overcome.

C. The Rejection is Also Overcome for Claims 49 and 41

Only claims 49 and 41 do not now include the exact language that the Office indicates to have priority to April 28, 1999. Applicants maintain that these claims also have priority to April 28, 1999, as set forth in their first response, which is incorporated herein by reference.

Nonetheless, even if claims 49 and 41 are not accorded the April 28, 1999 priority date, meaning that Brekken was available as prior art, the § 103(a) rejection is still overcome, including for the reasons set forth in Applicants' first response, which is incorporated herein by reference. Applicants respond to the second Action at pages 16-17 as follows.

Melton *does* teach that an antigen targeted by an ADEPT antibody should not circulate at "particularly high" levels (second Action at page 16), as this will act as a competitor for antibody binding. Particularly high blood levels of VEGF are known to be associated with various cancers, including breast, gastric, lung and colorectal cancers, thus teaching away from the invention. Applicants' first responses included Jinno *et al.*, *J. Gastroenterol.*, 33(3):376-82, 1998

(Exhibit K), to which the second Action's only reply is that this exhibit could not be located with Applicants' first response. As set forth above, an additional copy of Exhibit K, properly and timely submitted with Applicants' first response, has now been filed electronically. Therefore, upon consideration of Exhibit K, the Office will be able to agree that Melton teaches away from the invention and thus withdraw the rejection.

Presta concerns the humanization of the A.4.6.1 antibody, and shows the resultant humanized version to behave as A.4.6.1. As documented in numerous publications prior to Presta, it was well-known to those of ordinary skill in the art at the time of Presta, and prior to the present invention, that the A.4.6.1 antibody binds only to free VEGF. This was known because, as documented in numerous publications, A.4.6.1 was known to block VEGF binding to each of its receptors (see, *e.g.*, various references cited in Presta, including, for example, Kim *et al.*, *Growth Factors*, 7:53-64, 1992 (IDS Reference C29); and also Muller *et al.*, *Structure*, 6(9):1153-67, 1998 (IDS Reference C40)).

A direct consequence of A.4.6.1 blocking VEGF binding to each receptor is that A.4.6.1 cannot bind to VEGF docked in any receptor. These events are mutually exclusive (see, *e.g.*, **Exhibit C**, lower panels). Thus, it was well-known at the time of Presta, and prior to the present invention, that A.4.6.1 does not bind to VEGF docked in a receptor. This does not have to be overtly stated in Presta (second Action at pages 16-17) for it to be well-known at the time of Presta. Neither were these blocking characteristics of A.4.6.1 a discovery of the present inventors. Rather, they are summarized in the present specification in the context of well-known information from published literature (*e.g.*, specification at page 233; lines 17-20; lines 14-17; '432 application at page 165; lines 14-17).

Therefore, at the time of Presta, those of ordinary skill in the art knew that the A.4.6.1 antibody of Presta could not be used as a targeting agent, as it binds to only to free VEGF and

not to VEGF docked in any receptor (**Exhibit C**, lower panels). Indeed, A.4.6.1 and the humanized version of Presta are used only for anti-angiogenesis and not for vascular targeting. It thus remains uncontested that, by providing an antibody that cannot be used in ADPET, Presta *teaches away* from the proposed combination with Melton, which combination is therefore improper. Similarly, by providing an antibody that only binds to free VEGF, Presta also *teaches away* from the presently claimed invention, which requires an antibody that can bind to VEGF when VEGF is itself bound to a receptor.

The rejection is not rescued by the addition of Brekken. The only binding property of the 2C3 antibody described in Brekken is that it blocks VEGF binding to the VEGF receptor KDR/Flk-1 (VEGF receptor 2, VEGFR2) (**Exhibit C**, upper right panel). Therefore, Brekken also fails to describe an antibody that can bind to VEGF when VEGF is bound to a receptor. This property, which is important for ADEPT (**Exhibit C**, upper left panel), is not taught by Presta or Brekken. Neither do Presta or Brekken *suggest* that an antibody that blocks VEGF binding to VEGFR2 but not VEGFR1 could be generated. Indeed, Presta and the art as a whole teach away from such antibody by teaching that the A.4.6.1 antibody, which competitively inhibits VEGF binding to VEGFR2, <u>also</u> inhibits VEGF binding to VEGFR1 (most likely by steric hindrance). Accordingly, the property required for ADEPT is provided only by the present application, which teaches:

> "A particular advantage of the present invention is that the antibodies provided inhibit VEGF binding only to VEGFR2, and not VEGFR1. This <u>contrasts with</u> the leading antibodies in the prior art, including <u>A4.6.1</u>, which inhibit VEGF binding to both VEGFR2 and VEGFR1...A further advantage is that, <u>as binding of VEGF to VEGFR1 is maintained</u> in the presence of the antibodies of the invention, <u>they can be used to specifically deliver attached therapeutic agents to tumor vasculature by virtue of binding to VEGF that is bound to VEGFR1, which is upregulated on tumor endothelium</u>. In the context of immunoconjugates, therefore, the present invention provides agents that have both anti-angiogenic and tumor destructive properties within the same molecule.
>
> Specification at page 4, lines 15-30, emphasis added.

The cited Brekken paper does not teach or suggest the foregoing important antibody property, which was not published until after the priority and subsequent applications were filed (Brekken *et al.*, *Cancer Res,* 60:5117-5124, September 2000). The second Action comments that Brekken at page 1958 suggests that the 2C3 antibody is potentially a vehicle for targeting therapeutic agents to tumor connective tissue, *i.e.*, tumor stroma. However, independent claim 49, the only claim at issue, does not recite localization to tumor stroma, but only to tumor vasculature, which renders the second Action's position here moot[5].

As Brekken has been improperly combined with Melton and Presta, notably because Melton and Presta themselves teach away from the proposed combination, the § 103(a) rejection is unfounded and should be withdrawn. In any event, even if properly combined, the combination of Brekken, Presta and Melton still fails to teach or suggest the invention of claims 49 and 41 and fails to provide a reasonable expectation of success. In particular, neither Presta nor Brekken teaches or suggests the important antibody property, *i.e.*, that binding of VEGF to one VEGF receptor is maintained, the combination of Brekken, Melton and Presta does not suggest the claimed invention and does not provide a reasonable expectation of success.

In summary, the first § 103(a) rejection is thus overcome as to all claims for various reasons and should be withdrawn.

[5]The second Action also fails to address claim 51 that, even prior to the present revision, further distanced the invention from Brekken, Presta and Melton, even if all available as prior art and properly combined. Claim 51 still emphasizes the use of an immunoconjugate that binds to VEGF bound to the VEGF receptor VEGFR1 on endothelial cells of the tumor vasculature, thereby localizing the immunoconjugate to the tumor vasculature, which is particularly lacking in the combination of the cited references.

VIII. Rejection of Claims 5, 7, 29-31, 34 and 35 Under 35 U.S.C. § 103(a)

Lastly, claims 5, 7, 29-31, 34 and 35 remain rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over the forgoing Brekken, Melton and Presta references in further view of U.S. Patent No. 5,863,538 to ("the '538 patent"; Attorney Docket No. 3999.000700) and U.S. Patent No. 5,621,002 ("the '002 patent").

As set forth above (**Section III, Section VII,A**), the second Action accords a priority date of April 28, 1999 to current claim 5, and hence to all rejected claims, as claim 5 recites the very language that the second Action agrees has priority to April 28, 1999. Accordingly, Brekken is not available as prior art, as it has been removed by the *Katz* declaration of record. Thus, any § 103(a) rejection relying on Brekken is *prima facie* improper and should be withdrawn.

Again, even if Brekken was available as prior art, the § 103(a) rejection is still overcome for the reasons set forth in Applicants' first response, which are specifically incorporated herein by reference, and as detailed above. In particular, because Melton and Presta each teach away from the proposed combination, which combination is thus improper. Neither the '538 patent nor the '002 patent cure the deficiencies in the primary references, even if all available and properly combined, and the rejection is thus improper.

The second § 103(a) rejection is thus overcome and should be withdrawn.

IX. PTO Form-892

Applicants note that the Presta reference, cited in the two § 103(a) rejections, was not listed on the PTO Form-892 included with the first Action, which was not remedied in the second Action. Applicants therefore respectfully request that a new PTO Form-892 listing Presta be provided with the next communication from the Office.

X. Conclusions

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks and accompanying documents, and the guidance of the second Action on priority, the present claims are in condition for allowance and a timely indication to this effect is respectfully requested. Should Examiner Joyce have any questions or comments, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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